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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,344	06/09/2005	Guy Vergnault	28069-608N01US	3745

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EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
05/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,344	VERGNAULT ET AL.	
	Examiner	Art Unit	
	SHAWQUIA YOUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15-19 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-19 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 9/25/09.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12, 15-19 and 21-27 are currently pending in the instant application. Applicants have amended claims 1, 18 and 22, cancelled claims 14, 19 and 20 and added new claims 25-27 in an amendment filed on February 8, 2010. Claims 1-12, 15-19 and 21-27 are rejected in this Office Action.

I. *Response to Arguments/Remarks*

Applicants' amendment, filed on February 8, 2010, has overcome the rejection of claims 15-18, 22 and 24 under 35 USC 112, first paragraph for scope of enablement. The above rejection has been withdrawn.

Applicants traverse the rejection of claims 1-5, 8 and 14-24 under 35 USC 103 as being unpatentable over Stefano in view of Mueller, et al and Drug ank and of Mehnert, et al. and zur Mtihlen, et al. Applicants argue that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. Applicants further argue that combining references to produce spironolactone particles required by the claims was not predictable in view of the prior art. Applicants argue that the instant claims 1, 21 and 22 have been amended to include that the recited nanoparticle is stable. Applicants also argue that the teachings of the specification teach how to make the stable spironolactone formulations according to the invention and the stablility compared to prior art spironolactone formulations is illustrated in Example 2 and accompanying FIG 2. However, the Examiner wants to point out that nanoparticles

having a lipid crystal shell were already well known in the art and the advantages of using solid lipid nanoparticles for topical application (i.e., their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition, possibly to modulate drug release, etc.) as discussed in Mueller, et al. were also well known in the art. So modifying a well know formulation comprising spironolactone for topical application to skin or mucosa so that the formulation is a stable nanoparticle incorporated into a crystalline network system would be obvious and within one of ordinary skill in the art because the motivation to make the modification would be to prepare a improved formulation with the above stated advantages (i.e. their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition, etc.). The Examiner also wants to point out that one of the advantages of using solid lipid nanoparticles would be to have the ability to protect chemically labile ingredients against chemical decomposition which means that the formulation would be more stable. The Examiner wants to further point that the fact that the nanosuspension of spironolactone is more stable than the commercially available formulation of spironolactone in non-nanoparticulate is not considered unexpected results since the prior art already discussed that using solid lipid nanoparticles would be more stable because it has the ability to protect chemically labile ingredients against chemical decomposition as stated above. Applicants' amendment to claims 1, 21 and 22 by adding the term "stable" so that the invention is drawn to a stable nanoparticle formulation does not overcome the pending 103 rejection because the prior art already teaches that using nanoparticles would result in a more stable

formulation. Applicants' arguments have been fully considered but are not persuasive for the reasons stated above and the Examiner has maintained the 103 rejections.

II. *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on September 25, 2009 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

III. *Rejection(s)*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8,15-19 and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano (US 5,506,222) in view of Mueller, et al. in further view DrugBank (http://redpoll.pharmacy.ualberta.ca/drugbank) and of Mehnert,et al. and zur Mtihlen, et al.

Regarding claims 1 and 2, the instant Application is drawn to a formulation comprising spironolactone in an oriented crystalline lipid matrix for application to skin or mucosa. Stefano teaches spironolactone for topical application (column 11, claim 1) in a lipid matrix (column 12, claim 2, Substituted unsaturated fatty acids), but is silent regarding oriented crystalline nanoparticles. Mueller, et al. teaches solid lipid nanoparticles (50 to 1000 nm) for various applications such as topical (See page 162, section 2 and page 169, section 8) having a drug enriched core with a lipid crystal shell, formed as a function of the lipid's melting point and the relative solubilities of the drug and the lipid (See pages 164-167, section 3). The drug enriched core is formed when the drug precipitates before the lipid crystallizes. Because spironolactone (7a-acetylthio-3- oxo-17a-pregn-4-ene-21,17-carbolactone) is practically insoluble in water and has a Log P of 4.3 (See Drugbank entry for Spironolactone), the lipid nanoparticulate form of the drug forms such that the lipid crystal shell's hydrophilic "side" would face "outward," because the hydrophobic "side" would face "inward" toward the encapsulated lipophillic spironolactone. Mehnert, et al. (at Section 4.2 on page 179) further teaches that photon correlation spectroscopy is the state of the art measurement technique for particle size determinations of particles in the range of "a few nanometers to about 3 microns."

Because of the distinct advantages of using solid lipid nanoparticles for topical application (i.e., their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition, possibility to modulate drug release, etc.) it would have been obvious to the person of ordinary skill in the art at the time the invention was made to have combined the formulation taught by Stefano with the liquid

crystalline nanoparticulate lipid taught by Muller, et al obtain a topical dosage form of spironolactone with bioavailability resulting from the use of nanoparticulates.

Regarding claims 8, 15-19, 23 and 24, Muller, et al and Stefano are discussed above, with Stefano teaching the use of topical spironolactone compositions to treat the effects of increased androgenic activity including acne and hirsutism (abstract). These topical formulations comprise glyceryl monoesters, e.g. glyceryl monostearate (column 6, line 26), which are inherently crystalline under certain conditions of temperature, and other components of a cosmetically suitable cream base (column 4, lines 54 to 63) with additional excipients designed to promote drug delivery at the active site within the skin strata in order to obtain a therapeutic effect (column 5, Example 1 et seq.). Thus, it would have been obvious to the artisan of ordinary skill to combine the topical spironolactone formulation and dosing information of Stefano with the distinct advantages of using solid lipid nanoparticles for topical administration of Muller, et al. to treat the effects of increased androgenic activity (e.g., acne and hirsutism) in patients with a need for such treatment using a topical preparation.

Regarding claims 1, 21 and 22, Muller, et al, Mehnert, et al., and Stefano are discussed above, but they do not teach specific particles in the size range of from 300 to 900 nanometers. The adjustment of particular conventional working conditions (e.g., determining result effective particle sizes beneficially taught by the cited references, especially within the broad ranges recited in claims), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the

artisan of ordinary skill. Accordingly, this type of modification would have been well within the purview of the person of ordinary skill in the art and no more than an effort to optimize results. Also it was well established in In re Rose, 105 USPQ 237 (CCPA 1995), that selection of particle size is not a patentable modification in the absence of unobvious results.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Muller, et al. in further view of Sjoblom (Emulsions-a fundamental and practical approach, pages 64-65, 1992, Kluwer Academic Publishers). Stefano and Muller, et al. are discussed above with Stefano further teaching glycerol monoesters (e.g., glyceryl monostearate, column 6, line 26), but they are silent regarding lipid crystallization temperature. Sjoblom teaches lipids with a crystallization temperature in the recited range such as 1-monopalmitin with a crystallization temperature of 75.9 (page 65, table 2), and further teaches beta-crystal of the monoglycerides (pages 64-65). Adjustment of crystallization temperature by judicious selection of formulation components such as these monoesters or monoglycerides yields an extent of crystallinity useful in topical formulations of nanoparticulate spironolactone formulation and would have been well within the purview of a person of ordinary skill in the art at the time the invention was made.

Claims 6, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Muller, et al. in further view of Hansen (US 6,228,383 B 1) and Klein, et al. (US 6,013,637). Regarding claims 6 and 7, Stefano and Muller, et al. are

discussed above, but are silent regarding the solvent in which the nanoparticulate is formed. Hansen teaches that the lipid crystals are formed from polar liquids such as water and glycerol (column 6, lines 23 to 53), and that the lipid crystals are comprised of glyceryl monoesters of C1-8 fatty acids (Id.). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the nanoparticulates taught by Stefano and Muller, et al. with the solvent and lipid formulation components (specifically their inherent physical properties) taught by Hansen in order to obtain a product with the physical properties necessary to effect a solid state product at a temperature range suitable for typical topical cosmetic preparations.

Regarding claims 9-12, Hansen and Muller, et al. are discussed above with Hansen further teaching that the composition may be characterized as a suspension (column 14, line 46, thus in view of Muller, et al. a "nanosuspension") and that it further comprises a stabilizer (e.g., emulsifying agent, antioxidant, preservative, solubilizing agent, column 14, lines 52-67), which would have been an obvious addition to the formulation in order to maintain the suspension over the time and temperature ranges required to yield a useful product.

Hansen and Muller, et al. are both silent regarding sodium docusate as a stabilizer per se, but the person of ordinary skill in the art would recognize the term "stabilizer" as referring to any of a number of classes of compounds including surface active agents. Hansen teaches "solubilizing agents" (column 14, line 65), and as

indicated in Klein, et al, sodium docusate is a stabilizing agent used in topical pharmaceuticals (See column 2, lines 29-33 and column 4, lines 29-35). Thus, the claimed stabilizer is equivalent to the teachings of Hansen in view of Klein, et al.

IV. Objections

Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form. Claim 19 has the same limitation as claim 18 which is "wherein said condition is selected from the group consisting of acne, hirsutism, androgenic alopecia and rosacea.

V. Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Shawquia Young/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626